

Drug Design

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Alteration of Stereochemistry

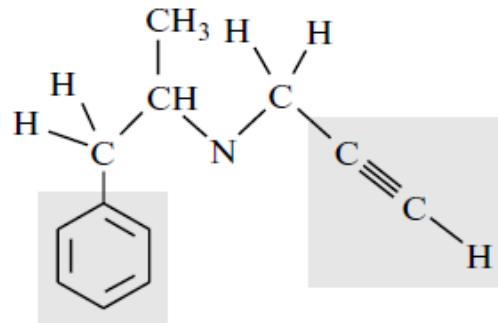
Stereochemistry and Drug Design

- The shape of a molecule is one of the most important factors that affect drug activity.
- So, the overall shape of the structure of a molecule is an important consideration when designing an analogue.
- Some structural features impose a considerable degree of rigidity into a structure whereas others make the structure more flexible.
- Other structures give rise to stereoisomers can exhibit different potencies, types of activity and unwanted side effects.
- The extent to which one can exploit these structural stereochemical features depends on our knowledge of the structure and biochemistry of the target biological system.

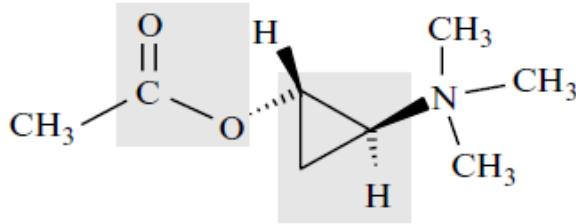
Alteration of Stereochemistry

Structurally Rigid Groups: nature and uses

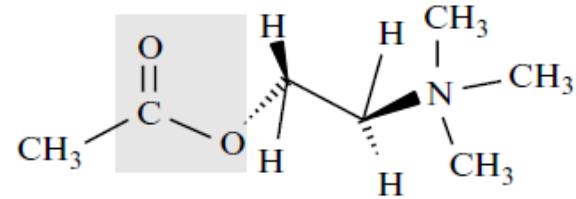
- Structurally rigid groups are unsaturated groups of all types (esters and amides, aliphatic conjugated systems and aromatic and heteroaromatic ring systems) and saturated ring systems.



Selegiline (MAO inhibitor)



1-Ethoxycarbonyl-2-trimethylaminocyclopropane
(Acetylcholine mimic)



Acetylcholine

- The binding of these rigid structures to a target site can give information about the shape of that site as well as the nature of the interaction between the site and the ligand.

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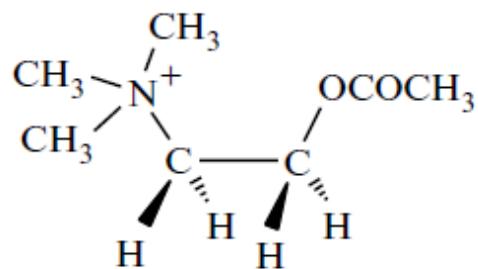
Structurally Rigid Groups: nature and uses

- Rigid structures may also be used to determine the conformation assumed by a ligand when it binds target site.
- The fact that the structure is rigid means that it may be replaced by alternative rigid structures of a similar size and shape to form analogues that may have different binding characteristics and possibly a different activity.

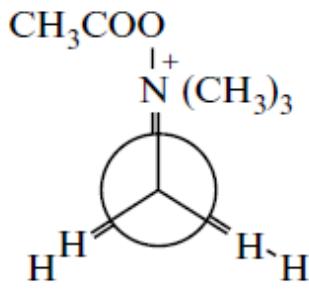
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Conformation (Conformational isomers)

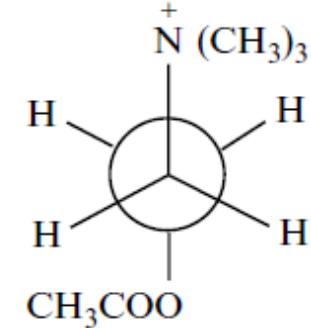
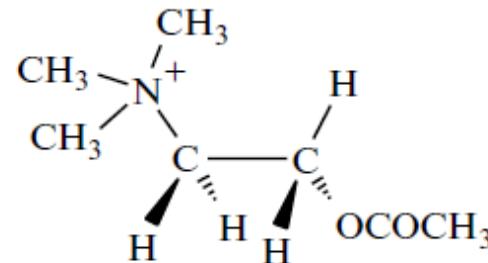
- The flexibility of the structures of both ligands and receptors accounted for the same ligand being able to bind to different subtypes of a receptor.
- A ligand assume different conformations when it binds to the different subtypes of the receptor. (Ach exhibits both muscarinic and nicotinic activity).



Syn-acetylcholine



Anti-acetylcholine

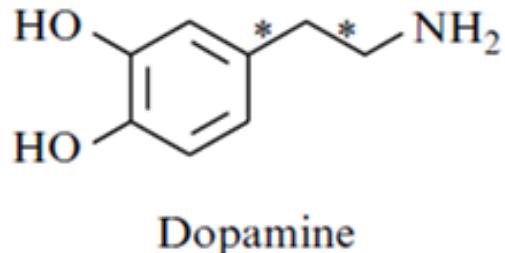


The muscarinic activity is due to anti (staggered) conformation
The nicotinic activity is due to the syn (eclipsed) form.

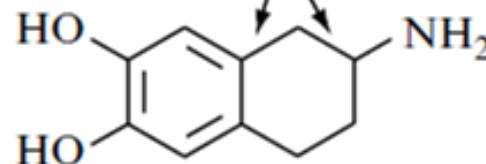
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Conformation (Conformational isomers)

- Using more restricted compounds that contained acetylcholine residue locked in the appropriate conformation by the ring could result in the selective binding of drugs to target sites that could result in very active drugs with reduced unwanted side effects.
- Small ring systems are usually the most popular choice for conformational restrictions .



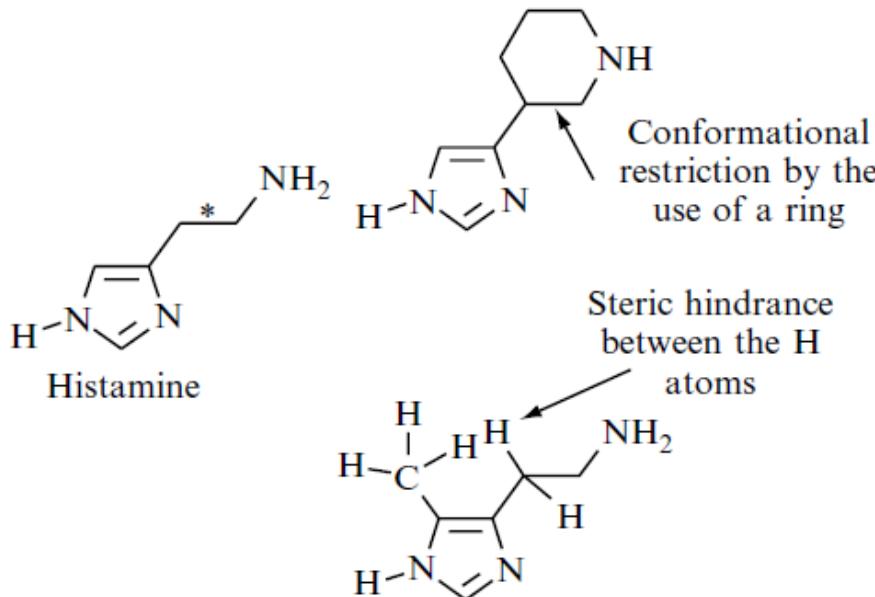
Conformational
restriction by the
use of a ring



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Conformation (Conformational isomers)

- In all cases the structures used must be chosen with care because there was always be the possibility that steric hindrance will prevent the binding of the analogue to the target.
- One limitation is to know which bond to restrict.



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Conformation (Conformational isomers)

- The biological data obtained from restricted conformation analogues can be of use in determining the most bioactive conformation of the ligand.
- If the analogue exhibits either the same or a greater degree of activity as the lead compound it may be concluded that the analogue has the correct conformation for binding to that site.
- However, if the analogue exhibits no activity, the result could be due to either steric hindrance between the restricting group and the target or the analogue having the incorrect conformation.
- In this case computer modeling may be of some assistance.

Alteration of Stereochemistry

Configuration

- The presence of configurational centers gives rise to geometric and optical isomerism.
- Because these stereoisomers have different shapes, biologically active stereoisomers will often exhibit differences in their potencies and/or activities.
- These pharmacological variations are likely when a chiral centre is located in a critical position in the structure of the molecule.
- So, it is now necessary to make and test separately all the individual stereoisomers of a drug.

Alteration of Stereochemistry

Design of Stereoisomers by Introduction of Chiral Center

- Optical enantiomers are chiral molecules with identical chemical and physicochemical properties, except their differences on the rotation of polarized light.
- Biologically, Chirality plays an important role in drug action.
- Receptors are chiral environments that discriminate between the different enantiomers of an optically active drug, as if they were different molecules.
- Stereochemical factors also influence the pharmacokinetics of the drugs, especially biotransformation.
- Today, the view of racemate as a mixture of one active desirable enantiomer (eutomer) and other inactive or even toxic antipode is not realistic.

Alteration of Stereochemistry

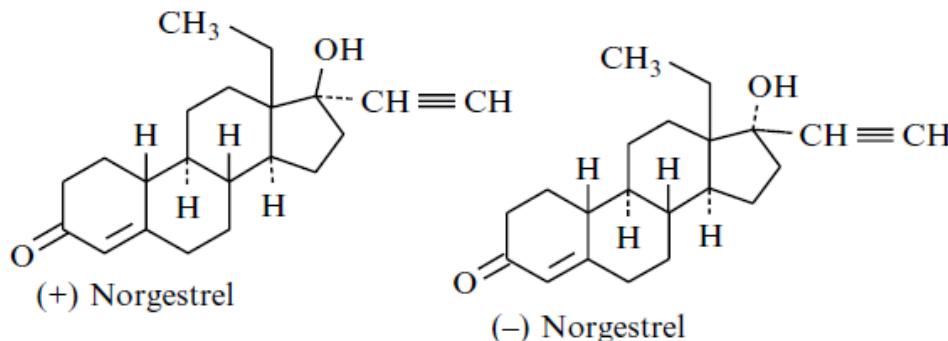
Design of Stereoisomers by Introduction of Chiral Center

- It is now appreciated that the “other” enantiomer may be inactive, active in the same way as the first enantiomer, antagonist to the first enantiomer, has a separate and desirable activity and/or responsible for some level of toxicity.
- Pure enantiomers are developed and introduced in the pharmaceutical market.
- The use of a single enantiomer has a number of advantages:
 - ✓ An improved therapeutic/pharmacological profile.
 - ✓ A reduction in complex drug interactions.
 - ✓ A simplified pharmacokinetics.
 - ✓ A novel therapeutic indication.

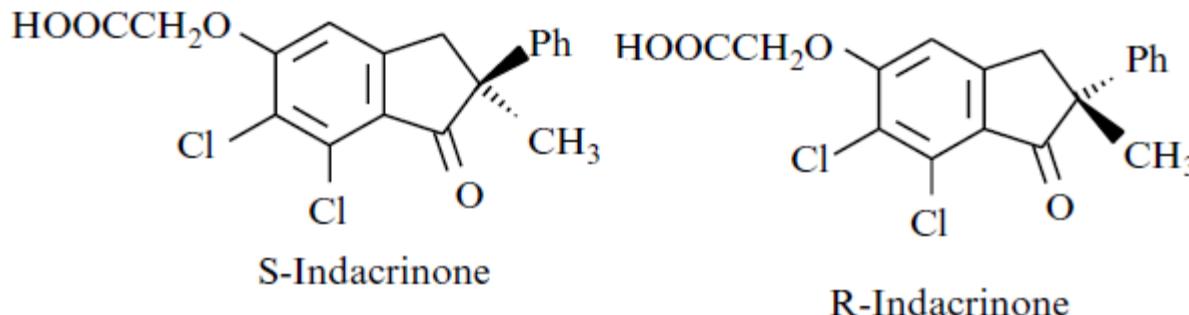
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Impact of Stereochemical factors on pharmacokinetics of drugs

- For example, (-)norgestrel is absorbed at twice the rate of (+)norgestrel through buccal and vaginal membranes.



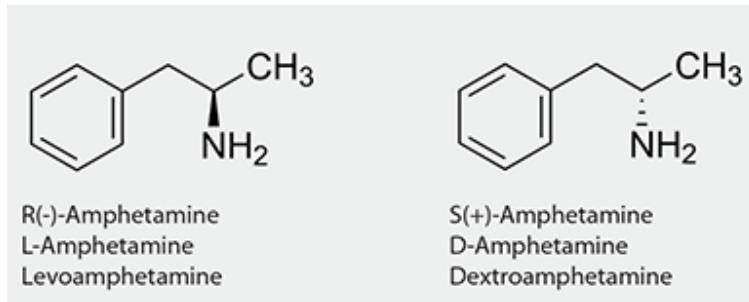
- The plasma half life of S-indacrinone is 2–5 hours whilst the value for the R isomer is 10–12 hours.



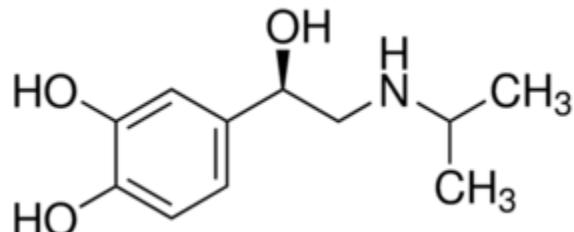
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Impact of Stereochemical factors on potency and SE of the drugs

- The dextrorotatory isomer of Amphetamine has the (S) configuration and produces fewer cardiovascular effects than the levorotatory (R)-isomer.
- Additionally, it is up to 10 times more potent than the (R)-isomer as an alerting agent and about twice as potent as a psychotomimetic agent.

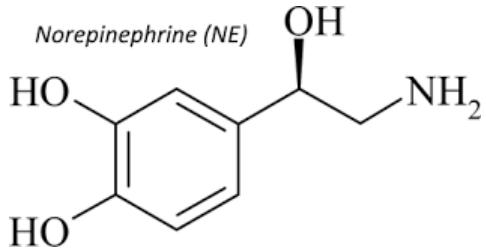


- R(-)-Isoprenaline is up to 800 times as a bronchodilator more than the S (+) isomer.

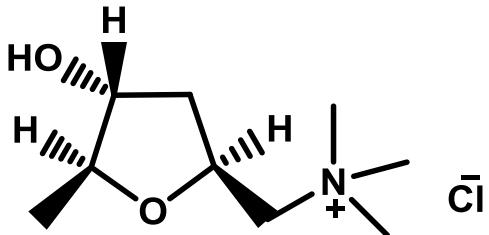


Alteration of Stereochemistry

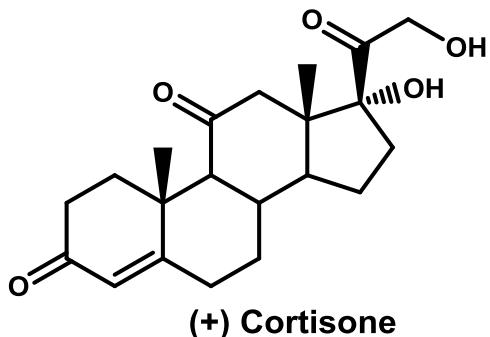
- R(-)-Norepinephrine is 70 times more active as a bronchodilator than (+) isomer.



- S(+) - muscarine has 700 times the muscarinic activity of R(-) isomer.

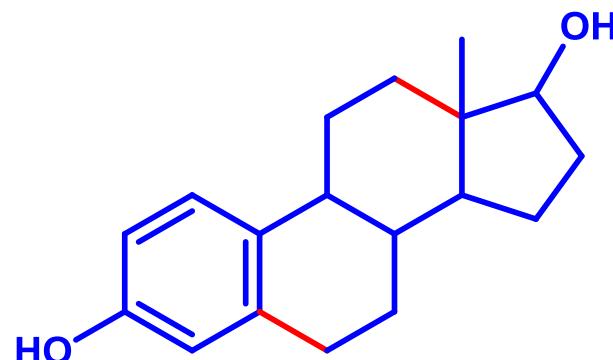


- (+)-Cortisone is active, while (-) cortisone is inactive.

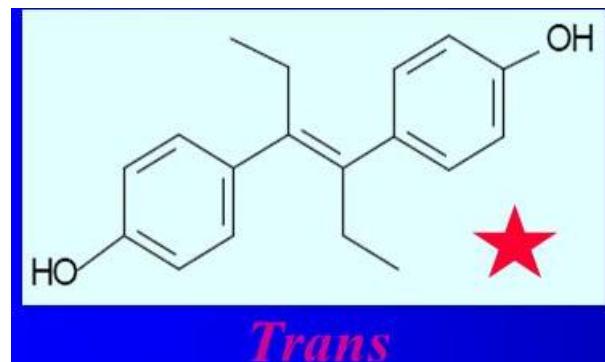


Alteration of Stereochemistry

- In diethylstilbestrol, the E-isomer (trans) has 10 times the estrogenic potency of the Z-isomer (cis).
- This effect has been rationalized because the E-geometric isomer looks as an open chain analog of the natural estrogen estradiol.



Estradiol



Trans



cis